BIOGRAPHICAL SKETCH

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NAME: Miller, Benjamin F, Ph.D.

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POSITION TITLE: Associate Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Wisconsin, Madison	B.S.	1995	Kinesiology
University of Wisconsin, Madison	M.S.	1998	Kinesiology
University of California, Berkeley	Ph.D.	2002	Integrative Biology
Institute of Sports Medicine, Copenhagen	Post-Doc	2004	Muscle Physiology

A. Personal Statement

I am the co-director (with Karyn Hamilton) of the Translational Research on Aging and Chronic Disease Laboratory (TRACD) within the Human Performance and Human Research Laboratory (HPCRL) at Colorado State University. Currently, the broad focus of TRACD laboratory is the regulation of stress resistance, mitochondrial biogenesis, and macromolecular turnover in the context of aging and chronic disease. The laboratory uses in vitro and in vivo animal models and translates findings through preclinical human trials. We are particularly interested in long-lived models to determine shared mechanisms of slowed aging. In this context, the maintenance of proteostatic processes seems to be key. For this project, Dr. Hamilton and I use our combined expertise of cell culture models (Hamilton) and stable isotope methods (Miller). In addition, we rely on provision of fibroblasts from our long-term collaborator, Rich Miller (University of Michigan), and instrumentation and computational support of our collaborators Dr. Ken Reardon (Dept. of Chemical and Biological Engineering, Colorado State University), Dr. Patrick Shipman (Dept. of Mathematics, Colorado State University), and Dr. John C. Price (Dept. Chemistry and Biochemistry, Brigham Young University). The assembled team ensures a high likelihood for successfully testing the hypotheses proposed for this R03 mechanism.

B. Positions and Honors

Positions and Employment

2004-2006 Lecturer, Department of Sport and Exercise Science, University of Auckland, Auckland, New Zealand
2005-2006 Honorary Member, Liggins Institute, New Zealand Center of Research Excellence, University of Auckland, New Zealand.
2007 – 2012 Assistant Professor, Department of Health and Exercise Science, Colorado State University, USA.
2007-Present Faculty Affiliate, Colorado State University Center on Aging, Colorado State University, USA.
2010-Present Affiliate Member, Center for Environmental Medicine, Colorado State University, USA.
2010-Present Faculty, Colorado School of Public Health, Colorado, USA.
2010-Present Graduate Faculty, School of Cell and Molecular Biology, Colorado State University, USA.
2012-Present Associate Professor, Department of Health and Exercise Science, Colorado State University, Fort Collins, CO

Other Experience and Professional Memberships

1998-Present Member, American College of Sports Medicine
2000-Present Member, American Physiological Society
2005-2006 Physiological Advisor, New Zealand Academy of Sport
2006-2007 New Zealand Nutrition Foundation's Older Persons Working Group
2009-Present Assistant Editor, Exercise and Sport Science Reviews
2006-2011 Associate Editor, European Journal of Sports Science
2012-Present Editorial Board, American Journal of Physiology-Endocrinology and Metabolism
2014-Present Editorial Board, Journals of Gerontology Series A, Biological Sciences
2014 –Present Associate Editor, Journal of Applied Physiology

Honors

2003 United States National Institute of Health Ruth L. Kirschstein Post Doc Fellowship- Turnover of Musculotendinous Collagen Following Exercise.
2004 American Physiological Society Young Investigator Award, Environmental and Exercise Physiology.
2006 NIA Summer Institute on Aging Research.
2006 Early Career Research Excellence Award, University of Auckland, New Zealand.
2008 Fellow, The American College of Sports Medicine
2010 NIH/NIA Summer Training Course in Experimental Aging Research
2010 Tenure Track Faculty Academic Excellence Award, College of Applied Human Sciences, Colorado State University
2010 NIH Loan Repayment Program – Renewal 2012, 2014

C. Contribution to Science

1. My earliest work was highlighted by a new technique that I developed called the lactate clamp. There was controversy in the literature about whether or not aerobic exercise training increases the gluconeogenic capacity of the liver. Part of the reason for this unknown was that increased aerobic capacity also diminished the circulation of gluconeogenic substrates so it was therefore hard to assess whether or not absolute capacity of the liver improved. The method we developed used an infusion of sodium lactate, a primary gluconeogenic substrate, so that we could "clamp" both non-exercise trained and exercise-trained human subjects at the same lactate concentration. Using stable isotopes, we found that indeed gluconeogenic capacity increased with exercise training. Since the development of this method, I have assisted many laboratories in modifying the lactate clamp for their own use. Perhaps most clinically important is that a group has adapted these methods to improve outcomes after traumatic brain injury (e.g. PMID: 25279664). Relevant publications:

A. **Miller, B. F**., Fattor, J. A., Jacobs, K. A., Horning, M. A., Navazio, F., Lindinger, M. I., & Brooks, G. A. (2002a). Lactate and glucose interactions during rest and exercise in men: effect of exogenous lactate infusion. *The Journal of Physiology*, *544*(Pt 3), 963–975. PMID: 12411539.
B. **Miller, B. F**., Fattor, J. A., Jacobs, K. A., Horning, M. A., Suh, S.H., Navazio, F., & Brooks, G. A. (2002b). Metabolic and cardiorespiratory responses to "the lactate clamp." *American Journal of Physiology. Endocrinology and Metabolism*, *283*(5), E889–E898. PMID: 12376315.
C. **Miller, B. F**., Lindinger, M. I., Fattor, J. A., Jacobs, K. A., LeBlanc, P. J., Duong, M., et al. (2005). Hematological and acid-base changes in men during prolonged exercise with and without sodium-lactate infusion. *Journal of Applied Physiology*, *98*(3), 856–865. PMID: 15475600.
D. Fattor, J. A., **Miller, B. F**., Jacobs, K. A., & Brooks, G. A. (2005). Catecholamine response is attenuated during moderate-intensity exercise in response to the "lactate clamp". *American Journal of Physiology. Endocrinology and Metabolism*, *288*(1), E143–7. PMID: 15328074.

2. During my post-doctoral research my interest moved to skeletal muscle. Although the synthesis of skeletal muscle protein was somewhat characterized, no one had yet distinguished between the contributions of the muscle fibers and the supporting extracellular matrix and tendon to overall synthesis rates. We therefore developed stable isotope methods to assess muscle fiber, extracellular matrix and tendon protein synthesis in human subjects. The primary outcomes from this initial study were that all three tissues had an increase in protein synthesis for up to 72 hours after a single bout of exercise. Second, the responses of the three

fractions mirrored each other so that the response was coordinated between myofibers, extracellular matrix, and tendon. Finally, the results demonstrated that extracellular matrix and tendon were dynamic tissues that responded favorably to mechanical loading and were not as inert as previously thought. The primary paper from this series (listed as "A" below) has been cited nearly 200 times. Importantly, these studies were extended to determine sex differences in musculoskeletal responses and provided new insight into sex-specific protein synthetic outcomes. Relevant publications:

A. **Miller, B. F**., Olesen, J. L., Hansen, M., Døssing, S., Crameri, R. M., Welling, R. J., et al. (2005). Coordinated collagen and muscle protein synthesis in human patella tendon and quadriceps muscle after exercise. The Journal of Physiology, 567. PMID: 16002437.
B. **Miller, B. F**., Hansen, M., Olesen, J. L., Flyvbjerg, A., Schwarz, P., Babraj, J. A., et al. (2006a). No effect of menstrual cycle on myofibrillar and connective tissue protein synthesis in contracting skeletal muscle. American Journal of Physiology. Endocrinology and Metabolism, 290(1), E163–E168. PMID: 16131512.
C. **Miller, B. F**., Hansen, M., Olesen, J. L., Schwarz, P., Babraj, J. A., Smith, K., et al. (2006b). Tendon collagen synthesis at rest and after exercise in women. Journal of Applied Physiology, 102(2), 541–546. PMID: 16990502.
D. **Miller, B. F.,** Ellis, D., Robinson, M. M., Rivera, J. D., Kjaer, M., & Langberg, H. (2010). Measurement of skeletal muscle collagen breakdown by microdialysis. Scandinavian Journal of Medicine & Science in Sports, 21(6), e1–e8. PMID: 20561272.
E. Hansen, M., Langberg, H., Holm, L., **Miller, B. F**., Petersen, S. G., Doessing, S., et al. (2011). Effect of administration of oral contraceptives on the synthesis and breakdown of myofibrillar proteins in young women. Scandinavian Journal of Medicine & Science in Sports, 21(1), 62–72. PMID: 19883384.

3. There has been much research into the loss of skeletal muscle mass and function with age (sarcopenia). Regarding exercise interventions, the focus is primarily on the use of resistance training. Using knowledge about how the cell adapts to different exercise and nutritional interventions, we reasoned that aerobic exercise in combination with protein feeding, would have benefits similar to resistance training. The use of aerobic exercise as our intervention was important since walking is the primary form of exercise in older individuals. Our series of studies highlighted that aerobic exercise, such as walking, could be used as a meaningful way to minimize the loss of skeletal muscle function with age. In addition, our work showed that energy balance is an important and often overlooked consideration when determining protein recommendations for older individuals. Relevant publications:

A. **Miller, B. F.** (2007). Human muscle protein synthesis after physical activity and feeding. Exercise and Sport Sciences Reviews, 35(2), 50–55. PMID: 17417050.
B. Jordan, L. Y., Melanson, E. L., Melby, C. L., Hickey, M. S., & **Miller, B. F**. (2010). Nitrogen balance in older individuals in energy balance depends on timing of protein intake. The Journals of Gerontology Series a: Biological Sciences and Medical Sciences, 65(10), 1068–1076. PMID: 20622139.
C. Murphy, C., & **Miller, B. F.** (2010). Protein consumption following aerobic exercise increases whole-body protein turnover in older adults. Applied Physiology, Nutrition, and Metabolism, 35(5), 583–590. PMID: 20962913.
D. Robinson, M. M., Turner, S. M., Hellerstein, M. K., Hamilton, K. L., & **Miller, B. F**. (2011). Long-term synthesis rates of skeletal muscle DNA and protein are higher during aerobic training in older humans than in sedentary young subjects but are not altered by protein supplementation. FASEB Journal, 25(9), 3240–3249. PMID: 21613572.
E. Minor, B. D., Heusinger, D. E., Melanson, E. L., Hamilton, K. L., & **Miller, B. F**. (2012). Energy balance changes the anabolic effect of postexercise feeding in older individuals. The Journals of Gerontology Series a: Biological Sciences and Medical Sciences, 67(11), 1161–1169. PMID: 22459620.

4. A stable isotope of an amino acid is the most widely used method to measure protein synthesis. The method usually includes 4-6 hour infusions followed by tissue sampling. There are a variety of shortcomings with this method including having to choose what 4-6 hour physiological state to measure in, and the necessity of using constant infusions thus limiting free living conditions. To circumvent these limitations, we have pioneered the use of deuterium oxide (^2H_2O) for long-term (2-6 week) measurements of protein synthesis in cells, animals, and humans. By using these methods, we have documented subtle differences that accumulate over time that otherwise would not be detected with traditional acute measurements. In addition, we have

demonstrated that differences demonstrated acutely do not necessarily result in changes over time because of other compensatory mechanisms. Recently, with mathematical modeling, we demonstrated that the use of acute measurements may actually bias outcomes to more rapidly and more abundant proteins and are therefore not indicative of the entire tissue protein pool. Our most important work in this area is focused on the proper assessment of mitochondrial biogenesis because of the important role mitochondria play in aging and most chronic disease. To this end, with deuterium oxide we have made fundamental contributions to the role of mitochondrial biogenesis in models of slowed aging and in human aging. Because of our work using deuterium oxide, several other laboratories worldwide have contacted us resulting in several new collaborations. Relevant publications:

A. **Miller, B. F**., & Hamilton, K. L. (2012). A perspective on the determination of mitochondrial biogenesis. AJP: Endocrinology and Metabolism, 302(5), E496–9. PMID: 22205627.
B. **Miller, B. F**., Robinson, M. M., Bruss, M. D., Hellerstein, M., & Hamilton, K. L. (2012). A comprehensive assessment of mitochondrial protein synthesis and cellular proliferation with age and caloric restriction. Aging Cell, 11(1), 150–161. PMID: 22081942.
C. Scalzo, R. L., Peltonen, G. L., Binns, S. E., Shankaran, M., Giordano, G. R., Hartley, D. A.,.. & **Miller, B. F**. (2014). Greater muscle protein synthesis and mitochondrial biogenesis in males compared with females during sprint interval training. FASEB Journal, 28(6), 2705–2714. PMID: 24599968.
D. **Miller, B. F**., Wolff, C. A., Peelor, F. F., Shipman, P. D., & Hamilton, K. L. (2015). Modeling the contribution of individual proteins to mixed skeletal muscle protein synthetic rates over increasing periods of label incorporation. Journal of Applied Physiology: 118(6), 655-61. PMID: 25593288.
E. **Miller, B. F**., Ehrlicher, S. E., Drake, J. C., Peelor, F. F., Biela, L. M., Pratt-Phillips, S., et al. (2015). Assessment of protein synthesis in highly aerobic canine species at the onset and during exercise training. Journal of Applied Physiology, 118(7), 811-7. PMID: 25614602.

5. Our most recent work is focused on the biological determinants of aging and how to slow the aging process. To do so, we examined a number of long-lived models to investigate common mechanisms among the various models. To date we have examined caloric restricted, rapamycin treated, Snell dwarf, and the novel crowded litter models. What emerged from these models is that increased proteostatic mechanisms are a shared feature of long-lived rodents. Importantly, using our stable isotope approach, we proposed a new method by which both long-term protein and DNA synthesis are measured to determine the contribution of protein synthesis to proteins in new cells versus replacing of existing protein structures (indicative of increased proteostatic processes). Importantly, these studies have steered us to a loci further downstream of mTOR as potentially the key component to slowing the aging process. Importantly, increased proteostatic mechanisms are a consistent finding among the long-lived models, while decreased mTOR activity is not. These studies will help inform new strategies for slowing the aging process. Relevant publications:

A. **Miller, B. F**., Robinson, M. M., Reuland, D. J., Drake, J. C., Peelor, F. F., Bruss, M. D., et al. (2013). Calorie restriction does not increase short-term or long-term protein synthesis. The Journals of Gerontology Series a: Biological Sciences and Medical Sciences, 68(5), 530–538. PMID: 23105041.
B. Drake, J. C., Peelor, F. F., Biela, L. M., Watkins, M. K., Miller, R. A., Hamilton, K. L., & **Miller, B. F**. (2013). Assessment of mitochondrial biogenesis and mTORC1 signaling during chronic rapamycin feeding in male and female mice. The Journals of Gerontology Series a: Biological Sciences and Medical Sciences, 68(12), 1493–1501. PMID: 23657975.
C. Drake, J. C., Bruns, D. R., Peelor, F. F., Biela, L. M., Miller, R. A., Hamilton, K. L., & **Miller, B. F**. (2014). Long-lived crowded-litter mice have an age-dependent increase in protein synthesis to DNA synthesis ratio and mTORC1 substrate phosphorylation. AJP: Endocrinology and Metabolism, 307(9), E813–21. PMID: 25205819.
D. **Miller, B. F**., Drake, J. C., Naylor, B., Price, J. C., & Hamilton, K. L. (2014). The measurement of protein synthesis for assessing proteostasis in studies of slowed aging. Ageing Research Reviews, 18:106-11. PMID: 25283966.
E. Drake, J. C., Bruns, D. R., Peelor, F. F., Biela, L. M., Miller, R. A., **Miller, B. F.,** &Hamilton, K. L. Long-lived Snell dwarf mice display increased proteostatic mechanisms that are not dependent on decreased mTORC1 activity. Aging Cell, 14(3), 474-82. PMID: 25720574.

URL to full list of published work (My Bibliography, US National Library of Medicine):
http://www.ncbi.nlm.nih.gov/sites/myncbi/1Fsqi_MFP5bkA/bibliography/42389791/public/?sort=date&direction=ascending.

D. Research Support (selected)

Ongoing Research Support

1R01AG042569-01A1. PIs **Miller, B.F.,** and Hamilton, K.L. 6/1/13 - 5/30/2018.
Translational Regulation of Mitochondrial Protein Synthesis.
The overall goal of this project is to understand the selective translation of mitochondrial proteins during periods of energetic stress.

Dairy Research Institute. PIs **Miller, B.F.,** and Hamilton, K.L. 10/1/13-12/30/15
Activation of Nrf2 by CLA in milk to decrease the anabolic resistance of aging.
The goal of this project is to restore the anabolic effect of feeding in older individuals by mitigating oxidative stress and chronic inflammation.

National Institute of Aging, NIA Interventions Testing Program **Miller**, Hamilton, McCord (Co-PI) 3/12 - ?
Protandim and lifespan extension
Through NIA we are testing a compound of five phytochemicals (Protandim) that activate Nrf2 and the antioxidant response element (ARE) for the purpose of lifespan extension. NIA is performing the experiment at three sites. This testing program is responsible for determining the lifespan extension effects of several compounds (such as Rapamycin).

Research Support Completed in the Last Three Years

1K01AG031829-01A1 **BF Miller** (PI) 3/15/2009 – 3/14/2014
Tissue-specific mitochondrial turnover with aging and energy restriction.
The overall goal of this project is to understand the effects of age and caloric restriction on mitochondrial biogenesis and mitochondrial protein turnover

United States Navy **BF Miller**, KL Hamilton, C Bell (CO-PI) 9/1/10 – 8/31/12
Rapid fitness gains with short-term sprint interval training and Nuclear Respiratory Factor (NRF) activator supplementation.
Goal is to determine the effects of short-term training and NRF activators on mitochondrial biogenesis and rapid fitness gains.